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Different pain sensations in photodynamic therapy of nodular basal cell carcinoma Results from a prospective trial and a review of the literature

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Basal cell carcinoma;
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Summary
Background: Pain is a major side effect of topical photodynamic therapy (PDT), a relatively new and non-invasive treatment for particular types of basal cell carcinoma (BCC). In this study, we sought to characterise in more detail the quality and intensity of pain associated with PDT. Furthermore, we studied if gender, tumour size and localization as well as different light sources with comparable wavelengths had an influence on the pain.
Methods: A total of 64 nodular BCCs in 55 patients, of which 48 BCCs underwent preceding debulking, were treated with 5-aminolevulinic acid (ALA-PDT). Two metal halogen light sources were randomly used. Pain assessment was performed using a visual analogue scale (VAS).
Results: All patients experienced pain during illumination and 41.8% after illumination. The mean pain intensity was 3.88 with most patients experiencing burning (82.5%) or stinging (36.8%) sensations. Illumination with the Medeikonos® light source was experienced less painful than the Waldmann® lamp (4.64 versus 3.40; $p = 0.027$). Gender as well as tumour localization and size did not alter the pain scores. Likewise, no differences were observed between patients who underwent debulking and those who did not.
Conclusions: Treatment of single BCCs with ALA-PDT rarely results in unbearable pain. However, the degree of pain can vary depending on the light source used. Further studies are needed to unravel the pathomechanisms underlying the development of pain in PDT in order to develop adequate solutions for this undesirable side effect.

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Introduction

With the rising incidence of basal cell carcinoma (BCC), the arsenal of treatment modalities is also expanding. Photodynamic therapy (PDT) is a relatively new treatment of basal cell carcinoma. However promising, its position in the spectrum of BCC treatment has not been established yet.

The therapy is based on activation of a topically applied photosensitizer (light-sensitive molecules). These molecules form various cytotoxic species, which will damage essential cellular components of neoplastic or dysplastic tissue, causing the cells to undergo apoptosis. Other mechanisms of PDT are necrosis by direct damage and targeting the surrounding vasculature. Furthermore, inflammatory and immune responses contribute to the damaging effect of PDT [1]. On cell level, mitochondria, lysosomes, plasma membranes and nuclei of tumour cells have been evaluated as potential PDT targets [2].

The traditionally most commonly used topical photosensitizer is 20% 5-aminolevulinic acid (ALA) cream that is converted into protoporphyrin IX (PpIX), which is the immediate precursor of heme. The accumulation of PpIX is increased in tumour tissue, as compared to normal tissue, because of increased permeability in tumour tissue [3–7]. A photosensitizer that is increasingly being used is the commercially available methylester 5-aminolevulinic acid (Metvix®, Galderma, Paris).

PDT successfully treats superficial BCCs (with clearance rates ranging from 68% to 100%) [8–12] and yields cosmetically excellent results [6,8,13]. It's a safe procedure with little side effects. One of the advantages of PDT is, that large fields of actinic keratosis or BCCs can be treated in one session, which especially can be an advantage for organ transplant patients, BCC-nevus syndrome patients and patients with multiple BCCs [14,15]. The use of PDT is also an advantage over surgical treatment in treating areas with poor wound healing, like BCC on the lower extremities and in elderly [5].

With PDT, the photosensitizer is applied with a wide margin around the tumour, but accumulation of PpIX will take place mainly in the tumour cells. Therefore, in contrast to the more conventional therapies, like surgical removal, cryotherapy and curettage, there is a selective destruction of the malignant cells with minimal damage of the surrounding healthy tissue. This tumour selectivity is a major advantage in patients with multiple superficial BCCs, in which you need to spare as much healthy skin as possible, as it might be needed for future reconstructions. Disadvantages of PDT are the lack of histological control and the time consuming aspect [5].

PDT is contra-indicated in pigmented BCCs, because of diminished penetration of the light in the tumour. However, a recent study has shown that PDT using a wavelength of 390 nm does penetrate into a pigmented BCC [16]. BCCs with other histological types than superficial or nodular BCC are contraindicated as well [5,17].

The major side effect of PDT, which is described in different studies, is the pain experienced during treatment. Most patients experience a stinging and/or burning sensation, usually mild or moderate [4,6,7,11,18,19]. Occasionally, the pain can be intolerable to certain individuals leading to cessation of the treatment. This is likely to occur more frequently when large fields or facial areas are treated [6].

Pain can occur both during and after treatment. The underlying mechanism of pain caused by PDT has not been unravelled so far, but several theories have been posed. These theories will be discussed further on in this article.

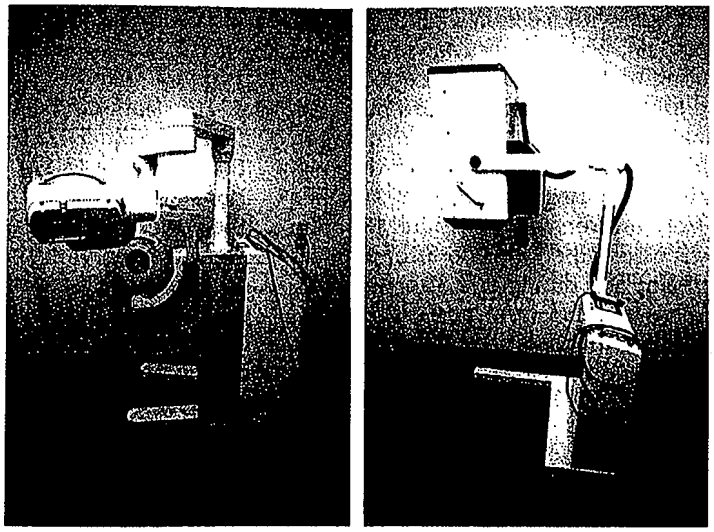
Immediately after illumination, erythema, oedema and crusting are common, which mostly resolves within 4 weeks after treatment [4,5, 17,20]. Sometimes, temporary hyperpigmentation is seen in the illuminated skin [21].

Literature search learns that the number of studies concerning the experienced pain during photodynamic therapy is limited. The objective of this study was to learn more about the character and intensity of the pain and to compare this to the literature. Furthermore, we wanted to investigate whether large size or certain localizations predispose to more pain. We also compared pain experienced with two light sources with comparable wavelengths, which are both currently being used in PDT practice.

Materials and methods

Study design

This study forms a part of a randomised controlled trial 'Long term results of topical photodynamic therapy versus conventional excision in the treatment of nodular basal cell carcinoma' in which patients with primary nodular BCCs were randomly treated with either conventional excision or ALA-PDT. The objective of this spin-off was twofold. The primary goal was to evaluate the pain assessment that was performed in all BCCs treated with ALA-PDT. We also compared two light sources



	Medeikonos	Waldmann PDT 1200
Kind of source	Metal halogen	Metal halogen
Treatment dose	10-150 J/cm^2	10-200 J/cm^2
Light intensity	40-100 mW/cm^2	10-200 mW/cm^2
Wavelength	580-680 nm	600-750 nm
Treatment area	10-10 cm	Ø 15 cm

Figure 1 Specifications light sources.

with comparable wavelengths (Medeikonos® and Waldmann PDT 1200®), which are currently used in daily practice. No formal randomisation was performed.

Patient selection

Patients between 18 and 85 years old, with previously untreated, histopathologically proven BCC of the nodular type, were recruited from the outpatient department of Dermatology of the University Hospital in Maastricht, The Netherlands. Patients were selected according to the following criteria: nodular, primary BCC, localized anywhere on the body except the eyelids, the lateral and medial canthus of the eyes and the ears, with a clinical diameter smaller than 20 mm. The exclusion criteria were: recurrent BCC, pigmented BCC, histological subtypes other than nodular, BCC-nevus syndrome, patients with hypersensitivity to red light or to 5-ALA cream, patients with porphyrea, manifest malignity, phototoxic/sensitive drugs, pregnancy and patients with more than 10 BCCs. Patients, medical history concerning pain medication was carefully noted. Informed written consent was obtained from all patients. Patients were informed about the pain assessment to be performed during treatment.

Treatment procedure

Partial debulking of the tumour was executed 3 weeks before treatment. All tumour tissue arising above the level of the skin was removed by curettage with a Stieffel® sharp curette (nr. 4). In some cases, where no tumour tissue arising above the level of the skin was seen, curettage was not performed.

After sticking a felt ring around the tumour, the 5-ALA cream was applied on the tumour including a 5 mm margin. The whole treated area was then covered with an occlusive polyurethane dressing (Tegaderm®) and a light protection layer (tinfoil). This all was fixated with bandage. After an incubation time of 4 h the bandage and surplus of cream was gently removed after which the area was illuminated with a broadband red light source with an intensity of 100 mW/cm^2 and a light dose of 75 J/cm^2. We made use of two broadband light sources that were available in our department (Medeikonos® AB, Göteborg, Sweden; Waldmann PDT 1200®, Waldmann Medical Technique, Munich, Germany), of which more details can be found in Fig. 1.

Pain assessment

In order to measure the pain intensity experienced by the patients during the PDT, a visual analogue

scale (VAS) was used with scores from 0 to 10, with 0 indicating no pain, and 10 indicating unbearable pain [22]. During or directly after treatment the patients were asked for the experienced pain during the illumination and also the character, duration and radiation of the pain. Character of the pain was rated as burning, stinging, throbbing, tingling or lingering. More answers were possible. Duration of the pain was assessed during and after application of the cream, and during and after illumination. Again, more answers were possible. Finally, patients were asked for radiation of the pain into the surrounding tissue.

Statistical analysis

Data were analysed using SPSS-PC for Windows version 11.0. Mean pain intensity scores between groups were compared using the independent Samples *T*-test or ANOVA. A *p*-value of 0.05 or less was considered to indicate statistical significance.

Results

In total, 68 BCCs were treated in 60 patients. More men than women were treated (33/60; 55% versus 27/60; 45%). In total, 64 BCCs were analysed (1 patient died before treatment and 3 patients were excluded from the study before receiving treatment because they eventually did not meet the inclusion criteria). The average age of the patients at the time of treatment was 63.3 years (S.D. = 13.8; range 24–83). Two patients used pain medication (Ibuprofen) on daily basis for a medical condition not related to BCC.

The mean size of the tumours was 8.95 mm (95%CI 9.94–7.97; S.D. = 3.95; range 3–20) by 7.52 mm (95%CI 8.33–6.72; S.D. = 3.22; range 3–20). Most of the tumours were located in the face (33/62; 53.2%). Five BCCs were located in the neck area (8.1%), 8 on the trunk on the anterior side (12.9%), 11 on the back (17.7%) and 5 on the lower extremities (8.1%) (Fig. 2). Most BCCs were treated with the Medeikonos® lamp (40/64; 62.5%) and 23 tumours were treated with the Waldmann PDT 1200® lamp (23/64; 35.9%). With one tumour this information was lacking. The distribution and size of the tumours were comparable between these two groups.

Pain scores (VAS) were completed in 57 cases (89.1%). The mean pain intensity was 3.88 (S.D. = 2.07; range 1–8). There were no patients who discontinued the treatment. Fig. 3 represents the VAS scores in a histogram.

Regarding the character of the pain, 35 patients selected 1, 20 patients selected 2, and 2 patients selected 3 possibilities. In most cases, the pain was experienced as burning ($n = 47$; 82.5%), in 21 cases (36.8%) as stinging, in 9 cases (15.8%) as tingling and in only a few cases as lingering ($n = 3$; 5.3%) or throbbing ($n = 1$; 1.8%). Concerning the duration of pain, 30 patients selected 1, 24 patients selected 2, and 1 patient selected 3 possibilities. All patients experienced the pain especially during illumination, 41.8% ($n = 23$) of the patients experienced the pain also after illumination and only a few patients experienced the pain also during ($n = 1$; 1.8%) or after application of the cream ($n = 2$; 3.6%). The question whether radiation of pain existed was answered by 55 (85.9%) patients. In most cases, no radiation was mentioned, but in some cases (4/55; 7.3%) radiation

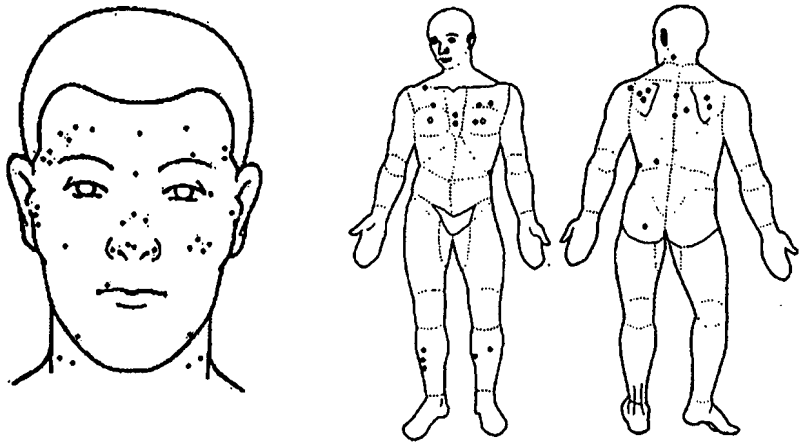


Figure 2 Distribution of tumours.

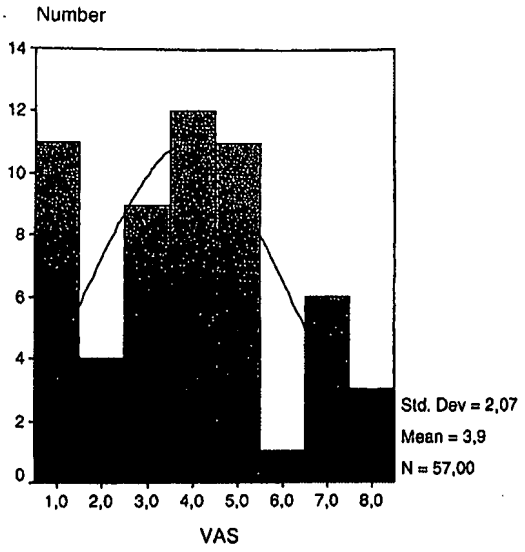


Figure 3 Distribution of VAS scores.

into the direct surroundings was reported. These tumours were all located in the face, two on the cheek, one on the upper lip and one on the nose.

The mean pain score in men (3.63; S.D. = 2.08) was not statistically significantly different from the pain score in women (4.15; S.D. = 2.07; $p = 0.353$).

When comparing the two broadband light sources, we found a difference in favour of the Medeikonos® device (3.40; S.D. = 2.19 versus 4.64; S.D. = 1.65). This is a statistical significant difference ($p = 0.027$).

We looked at the pain intensity of patients in relation to their age. The patients were dichotomised by age. The mean pain score for patients under 65 ($n = 30$) was 3.70 (S.D. = 1.78) for patients older than 65 years ($n = 27$) was 4.07 (S.D. = 2.37) ($p = 0.501$).

No statistical significant difference was seen between pain scores from patients who were treated in the facial/neck area ($n = 34$; mean 3.97; S.D. = 2.21) and patients who were treated on the trunk or extremities ($n = 21$; mean 3.67; S.D. = 1.96; $p = 0.607$). Of all localizations, regarded separately, only the nose seems to be more painful (mean 5.83).

Patients were also divided into two groups based on size of the tumour. No statistical significant difference between the mean pain score from patients with small tumours (1—10 mm; $n = 40$; mean 4.10; S.D. = 2.06) and patients with large tumours (>10 mm; $n = 15$; mean 3.20; S.D. = 2.15; $p = 0.159$) was found.

Prior to treatment, 48 tumours underwent tumour debulking, in 8 tumours this was not performed, and in one case, this information was missing. The mean pain score for the patients that underwent debulking (3.88; S.D. = 2.12) was not statistically significant different ($p = 0.877$) from the mean pain score for the patients who were not curetted (3.75; S.D. = 1.98).

In order to investigate whether there is a relation between the pain and the efficacy of the treatment, we looked at the pain scores of the patients in which the tumour was not cleared completely or had recurred ($n = 9$). The mean pain score in these patients was 3.50 (S.D. = 2.33) compared to mean pain score of 4.07 (S.D. = 2.12) in the patients that had no recurrence. This difference did not reach a statistical significance ($p = 0.495$).

Discussion

In literature, pain is considered to be a major side effect of ALA-PDT for BCCs and actinic keratosis. The pain intensity experienced in this study, on a VAS-scale from 0 to 10, had a mean value of 3.88. This mean VAS score during irradiation is comparable with rates of 2.30—4.38 reported in other studies (Table 1). The group of patients who received ALA-PDT in this study was, compared to those other studies, much larger. It is difficult to interpret the pain experienced by patients during photodynamic therapy because pain is a rather subjective feeling and because of the large inter-patient variation. But it is apparent from this study that ALA-PDT never resulted in unbearable pain when used in single, nodular BCCs.

As described in literature, most patients experienced the pain as burning and some also as stinging. All patients experienced the pain during illumination and some did directly after treatment as well. Only a few patients experienced radiation of the pain, but this was not distributed within a dermatome or in the area of a large nerve.

Interestingly, our results imply that lower pain intensities are experienced when the Medeikonos® light source is used. This has not been described in the literature before, as different light sources with comparable wavelengths have not been compared before in pain sensation. The difference in pain intensity between the two light sources cannot be explained by differences in wavelength or size of the illumination field, as they are comparable. The only difference is that Medeikonos® has an internal ventilator for cooling of the apparatus. It seems valuable in future to compare pain induced by PDT with metal halogen broadband light sources to the newer generation LED-based light sources.

Table 1 Studies reporting pain intensity in PDT

Author	N	Photosensitizer	Illumination (mW/cm²)	VAS	Lesions	Analgesia	Other findings
Grappengiesser, 2002 [6]	31	ALA	50–130	3.5	BCC	EMLA	Larger lesions more painful Lesions on head more painful
Wiegell, 2003 [7]	20	ALA	90	4.2	Normal skin	–	ALA more painful than MAL
		MAL		2.7			
Ericson, 2004 [25]	32	ALA	30	2.9	AK	–	No difference between fluence rates
			45	3.5			
			50	2.8			
			75	3.6			
Holmes, 2004 [19]	24	ALA	70–90	4	BCC, AK and BD	Tetracaine	No effect of tetracain gel
				4.5		Placebo	
Kuijpers, in press	32	ALA	100	4.38	BCC	–	–
		MAL		2.84			
Present study	57	ALA	100	3.88	Nodular BCC	–	Medeikonos light source less painful than Waldmann PDT1200

ALA: 5-aminolevulinic acid; MAL: 5-aminolevulinic acid methylester; AK: actinic keratosis; BD: Bowen's disease.

There were also no differences in localization, size or debulking of the tumour between the two groups.

In contrast to the study of Grapengiesser et al. [6], we were not able to detect a significant difference between the pain experienced during photodynamic treatment of facial lesions compared to PDT of lesions on the trunk or extremities. Possibly, the number of patients treated with PDT in this study was too small, however, still larger than in studies where a difference was recorded. It does seem that ALA-PDT is more painful on the nose ($n = 6$, mean 5.83, S.D. = 2.56) but we cannot draw any strong conclusions because the number of patients is too small to perform a proper statistical analysis.

In theory, treatment of large tumour areas with PDT is likely to lead to more pain than treatment of smaller areas, as was found in another study [6]. With our results, we found no statistical significant difference between treatment of small and larger lesions. Maybe this can be explained by the fact that in this study we only treated relatively small BCCs (up to 20 mm). More comparative studies are needed to investigate whether treatment of larger lesions is more painful.

There seems to be no difference in pain experience between men and women, in contrast to Grapengiesser et al. [6], who made use of Waldmann PDT 1200® as well. In their study, men experienced more pain than women. We found a somewhat higher pain score in women, although not statistically significant.

Comparing the pain scores of patients who underwent debulking before treatment and who did not receive curettage, we found no statistically significant difference. The debulking was performed 3 weeks before ALA-PDT and in this period the wounds resulting from the debulking procedures are likely to be healed. So, possible differences in pain scores cannot be explained by the application of an acid cream onto a fresh wound.

Photodynamic therapy often is regarded as a painful procedure. In some cases it requires interventions for pain control including application of ice, use of a fan, interruption of treatment, forced cooled air, and topical and oral analgesia [4,19,20]. Pain seems to be more of an issue with PDT than it does with other treatments of BCCs. The fact that pain in other treatments occurs at other stages of the procedure is probably often overlooked. With other treatments such as conventional excision,

there is pain experienced while giving the anaesthesia. Some patients also experience the removal of the sutures as painful. Perhaps there is a limited amount of pain expected and thus accepted in non-invasive treatments other than in invasive treatments where pain is expected. Rhodes et al. [13] compared PDT with conventional excision, but did not quantify the intensity of pain on a standardized pain score. They found that unlike surgery, there was no routine need for local anaesthesia. The pain with PDT was described as mild or moderate and resolving the same day without the need for medical intervention. In order to compare not only efficacy but also side effects as pain, comparative studies are needed, in which pain in PDT is compared to pain in other treatments, preferably with intra-patient (left–right) comparisons.

Our experience is that explanation of the procedure to the patients and reassurance is helpful. Possibly, patients are anxious for a new treatment and therefore more susceptible to pain.

It is often stated that patients contributed their experienced pain to the heat produced by the lamp. A study by Orenstein et al. [23] showed that irradiation of normal skin without ALA application was not accompanied by any pain even when the temperature was 44–45 °C.

Pain during treatment is supposed to be a result from a combination of intense nerve stimulation by reactive oxygen species and hyperthermia [20]. Another theory is that ALA is taken up by γ-aminobuturic acid (GABA) transporters into the peripheral nerve endings [7,24]. The discomfort post-treatment is more typical of an inflammatory process [17]. Treatment of large tumour areas and well-innervated anatomical locations such as the face and hands seems to result in more intense pain than treatment of smaller areas or other locations. Also, treating actinic keratosis is reported to be more painful than treating BCC.

Unlike ALA, methylester 5-aminolevulinic acid (MAL) is not transported by GABA transporters into the peripheral nerve endings. This may explain the clinical experience of more intense pain reactions observed during PDT after application of ALA as compared to MAL [7], which also has been confirmed in a recently performed study (Kuijpers et al., in press).

More research is required to unravel the mechanism of pain in photodynamic therapy, to adequately search for solutions in the combating of this problem. In this study we only included nodular BCCs, but with a view to the pain mechanism, it can be of great value to examine superficial BCCs as well.

Conclusions

Patients experience pain when treated with photodynamic therapy. The intensity of this pain in this study ranges from 3.5 to 4.6 on a VAS scale from 0 to 10. This is comparable with earlier findings in literature.

Concerning pain, single nodular BCCs up to 20 mm with prior tumour debulking can be well treated with photodynamic therapy without cessation of the treatment.

No statistical difference was found in size and localization of the tumours in pain intensity. Photodynamic therapy with the Medeikonos® light source appeared to be less painful than with the Waldmann PDT 1200® light source. To confirm any differences between various light sources, more studies are needed.

While PDT is often regarded as a painful treatment, there is not much knowledge about how this pain compares to other treatments. Comparative studies are needed to further investigate this.

The underlying mechanism of pain caused by PDT has not been elucidated so far. More research is needed to gain more insight in this mechanism, which may lead to a lead to a possible solution in analgesia for PDT.

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